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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/427,657	10/26/1999	KARI ALITALO	28967/35061A	3588

7590 10/02/2003

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1636	25

DATE MAILED: 10/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/427,657	ALITALO ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-18 and 21-100* is/are pending in the application.

4a) Of the above claim(s) *21,33-48 and 59-62* is/are withdrawn from consideration.

5)☐ Claim(s) *18* is/are allowed.

6)☒ Claim(s) *1-8,10-17, 22-32, 49-58, 63-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/05/02 has been entered.

▶ *Applicants are required to follow Amendment Practice under revised 37 CFR §1.121 (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm).*

Election/Restrictions

Applicant's election with traverse of Group I, Claims 1-8, 10-18, 22-32, 49-74 and 75-100 in Paper No. 23 is acknowledged. The traversal is on the ground(s) that the patentably distinct inventions should be restricted only if examination would pose serious burden on the examiner. The applicant further argues that enclosed declaration evinces the usefulness of VEGF-D in the treatment of restenosis by demonstrating its ability to reduce the intimal thickening of an artery following balloon -denudation. This is not found persuasive because VEGF-C (SEQ ID NO:1 encoding the amino acid sequences SEQ ID NO:2) and VEGF-D (SEQ ID NO:3 encoding the amino acid sequences of SEQ ID NO:4) are structurally and functionally distinct polypeptides which have different modes of operation, different functions, and/or different effects. Furthermore searching of group I would not fully anticipate the subject matter of group II and therefore would require additional search. For example, search of a nucleotide sequences encoding VEGF-C would not anticipate the nucleotide and/or polypeptides encoding the VEGF-D. Thus there is serious search burden to examine the invention of Group I and II together.

The requirement is still deemed proper and is therefore made FINAL.

Claims 21, 33-48 and 59-62 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 23.

Claim Objections

Claims 22, 26-29, 49, 57-58, 70-71 are objected to because of the following informalities: The instant claims contains non-elected subject matter (VEGF-D). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8,10-17, 22-32, 49-58, 63-100 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a mammalian subject to inhibit restenosis of a blood vessel by administering to the subject at the site of restenosis a replication-defective adenovirus vector comprising a polynucleotides sequences encoding VEFG-C polypeptide (SEQ ID NO:2), does not reasonably provide enablement for a method of treating restenosis by administering a nucleic acid sequence which encodes any portion or variant of amino acid sequences of SEQ ID NO:2, wherein the nucleic acid is administered using any viral or non viral vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature Of Invention:

The invention relates to a method of gene therapy.

Breadth Of Claims and Guidance Provided in the Specification:

The scope of invention as claimed encompasses the treatment of restenosis by administering any viral or non-viral vector comprising a polynucleotide sequence, which encodes

the VEFG-C polypeptide. The scope of invention as claimed further encompasses the use of any VEGF-C sequence and any unknown allelic form of VEGF-C. In addition the scope of invention as claimed encompasses a kit or formulation to treat restenosis comprising a nucleic acid sequences that promotes the expression of VEGF-C in cells of a blood vessel.

At best the specification teaches the use of adenovirus-mediated VEGF-C gene transfer in rabbit restenosis model The specification teaches an adenovirus vector containing the cDNA encoding the complete human prepro-VEGF-C open reading frame operably linked to CMV promoter and human growth hormone polyadenylation signal sequence. The specification further teaches balloon denudation of rabbit aorta followed by adenovirus mediated gene transfer after 3 days. The specification concluded that VEGF-c gene transfer significantly reduced intimal thickening at two weeks time point after aortic denudation and after vessel wall damage caused by the gene transfer catheter with out balloon denudation (Spec. pages 25-28 example-1).

However the specification fails to disclose that the gene transfer of a portions of SEQ ID NO:2 which comprises amino acid 30-131 and 211-419 of SEQ ID NO:2; a polypeptide sequence which lack amino acids 228-419 of SEQ ID NO:2; a polypeptide sequence which lacks amino acid 32-102 of SEQ ID NO:2 inhibits restenosis in a mammalian subject. Furthermore the specification fails to disclose that any unknown of allelic form of VEGF-C (nucleotide sequence which hybridizes the nucleic acid encoding the amino acid sequence of SEQ ID NO:2) would inhibit the restenosis of blood vessel in a mammalian subject. At best the specification only teaches an adenoviral-mediated-VEGF-C gene transfer. The specification fails to disclose that the administration of any other viral or non-viral vector would successfully deliver the VEGF-C gene to the cells of a blood vessel for the inhibition of restenosis.

State Of Art And Predictability:

Gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy. (Rosenberg et al, Science 287:1751, 2000, Verma, Mol. Ther. 1: 493, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997, Touchette, Nat. Med. 2(1) 7-8, 1996). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. For

example, in original clinical trial to treat adenosine deaminase (ADA) deficiency, patients received a total of 11 infusions of genetically modified autologous T-lymphocytes along with polyethylene glycol (PEG)-ADA. After 7 years of therapy no definitive conclusion is drawn as to the contribution of gene therapy to the present state of health of patients (Touchette, page 7 col.3, para.1; Anderson page 29 col.1, para.6). Furthermore, it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors (Verma et al, see page 239 col.3 par.2, page 242, table-2). Although the retroviral vectors are the vectors of choice, they require target cells to be in cycling state for the successful delivery of gene of interest. On the other hand vector comprising DNA viruses and liposome coated DNA have been used to transduce non dividing cells but this results in a transient expression due to non-integration of transgenes in host cells (Verma et al page 242, table-2). In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacle to overcome. The viral particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets (Anderson WF, page 25 col.2, para.4). In instant case besides an adenoviral vector the specification fails to disclose the use any other viral or non-viral vector that resulted in expression of VEGF-C in blood vessels to treat restenosis. Furthermore the pathophysiology of restenosis is incompletely understood and the technical barriers to achieving robust intra coronary gene transfer have not been overcome. For example it is unpredictable that a retroviral vectors would be able transfect non dividing blood vessels cells in the treatment of restenosis, since the retroviral vectors only infects actively dividing cells. (DeYong et al Circ Res 82;306-313, 1998 page 309, col.1).

Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success (Touchette page 7, col.1 para. 2; page 8, col.2 para 1-4). The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease. (Touchette, page 7, col.3, para.3). VEGF-C binds to VEGFR-2 and VEGFR-3 and has been show to stimulate both angiogenesis and

formation of lymphatic blood vessels (Hiltunen et al Circulation 102:2262-2268, 2000). In instant case the specification fails disclose that gene transfer of a portion of SEQ ID NO:2 (as claimed) would inhibits restenosis of a blood vessel. It is well known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The segments or variants of VEGF-C as claimed are mere hypothetical polypeptide because no biological function has been established. The mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. Therefore, Applicant has not presented enablement commensurate in scope with the claims which encompasses a portion or variant of SEQ ID NO:2. see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976).

Conclusion:

In instant case gene based therapies are not considered routine in the art and without sufficient guidance to a specific therapeutic gene the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. The undue experimentation required would include making any viral or non viral vector encoding any segments or variant of SEQ ID NO:2 (as claimed). The undue experimentation required would further include evaluation of inhibition of restenosis by each segment or variant of SEQ ID NO:2.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 29, 71-72, 98 and 100 are rejected under 35 U.S.C. 102(b) as being anticipated by Alitalo (W/O 97/05250, ref of record).

The instant claims are directed a kit or a formulation, which essentially are nucleotide sequences or vectors encoding the polypeptide VEGF-C. The labels and instructions do not contribute any essential patentable feature to the invention.

Alitalo teaches nucleotide sequences which matches 100% to the nucleotide sequence of SEQ ID NO: 1 which encodes the amino acid sequence of SEQ ID NO:2 (VEGF-C). The cited art further teaches human VEGF-C cDNA inserted in an expression vector (page 49 example-11). The cited art further teaches that VEGF-C polypeptide stimulates the tyrosine phosphorylation fo VEGFR-3 and VEGFR-2 receptors (page 57 lines 30-35). Therefore the cited art clearly anticipate the invention as claimed.

Response to arguments

The applicant argues that when printed matter is part of invention it is improper to ignore the printed matter in determining patentability (*In re Gulack*, 703 F.2d 1381 (Fed. Cir. 1983). The applicant argues that printed matter in instant case does recites an unobvious functional relationship in that it directs a medical application for the polynucleotides that was never suggested before (response pages 5-6 received 12/05/02).

While the legal standard is correctly stated, the applicant misapplies this standard to the current facts. In *Gulack*, the printed matter at issue was part of the substrate itself, not simply instructions on how to use the product of interest. As the *Gulack* Court noted "Where the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of Patentability." *In re Gulack*, 703 F.2d 1381, 1385 (Fed.

Cir. 1983). In *Gulack*, the printed matter is physically located on the band itself. In the current case, the instructions are not written out in the genetic code, nor are the nucleic acids related in any functional way to the instructions. The instruction on label are not necessary to use the products claimed, since, as shown by the prior art rejections, Alitalo use the same product. Unlike *Gulack*, where it would be impossible to form the claimed substrate without the printed matter and achieve the same functionality in the invention, in the current case, it would be easy to do so.

A kit which simply contained the nucleic acids would have the completely identical functionality of the kit which had the instructions and contained the nucleic acids. The composition is physically the same it must have the same properties. "Products of identical chemical composition can not have mutually exclusive properties."A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) see MPEP § 2112.02. Thus the invention as claimed is clearly anticipated by the cited prior art of record

Conclusion

Claim 18 is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
PATENT EXAMINER

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